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### Authors

Reilly, Karlyne M  
Kim, AeRang  
Blakely, Jaishri  
et al.

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COMMENTARY

# Neurofibromatosis Type 1–Associated MPNST State of the Science: Outlining a Research Agenda for the Future

Karlyne M. Reilly\*, AeRang Kim\*, Jaishri Blakely, Rosalie E. Ferner, David H. Gutmann, Eric Legius, Markku M. Miettinen, R. Lor Randall, Nancy Ratner, N. L. Jumbé, Annette Bakker, David Viskochil, Brigitte C. Widemann, Douglas R. Stewart

**Affiliations of authors:** Rare Tumor Initiative (KMR), Laboratory of Pathology (MMM), and Pediatric Oncology Branch (BCW), Center for Cancer Research, National Cancer Institute, Bethesda, MD; Center for Cancer and Blood Disorders, Children's National Medical Center, Washington, DC (AK); Department of Neurology, Johns Hopkins Hospital, Baltimore, MD (JB); Neurofibromatosis Center, Department of Neurology Guy's Hospital London, London, UK (REF); Department of Neurology, Washington University School of Medicine, St. Louis, MO (DHG); Department of Human Genetics, University of Leuven, Leuven, Belgium (EL); Hunstman Cancer Institute, University of Utah, Salt Lake City, UT (RLR, DV); Division of Experimental Hematology and Cancer Biology, Department of Pediatrics, Cincinnati Children's Hospital, University of Cincinnati, Cincinnati, OH (NR); Bill and Melinda Gates Foundation, Seattle, WA (NLJ); Children's Tumor Foundation, New York, NY (AB); Clinical Genetics Branch, Division of Cancer Epidemiology and Genetics, National Cancer Institute, Rockville, MD (DRS).

\*Authors contributed equally to this work.

**Correspondence to:** Douglas R. Stewart, MD, 9609 Medical Center Drive, Rm 6E450, Bethesda, MD, 20892 (e-mail: drstewart@mail.nih.gov).

## Abstract

Malignant peripheral nerve sheath tumor (MPNST) is an aggressive soft tissue sarcoma for which the only effective therapy is surgery. In 2016, an international meeting entitled “MPNST State of the Science: Outlining a Research Agenda for the Future” was convened to establish short- and long-term research priorities. Key recommendations included the: 1) development of standardized, cost-efficient fluorodeoxyglucose positron emission tomography and whole-body magnetic resonance imaging guidelines to evaluate masses concerning for MPNST; 2) development of better understanding and histologic criteria for the transformation of a plexiform neurofibroma to MPNST; 3) establishment of a centralized database to collect genetic, genomic, histologic, immunohistochemical, molecular, radiographic, treatment, and related clinical data from MPNST subspecialty centers in a standardized manner; 4) creation of accurate mouse models to study the plexiform neurofibroma-to-MPNST transition, MPNST metastasis, and drug resistance; 5) use of trial designs that minimize regulatory requirements, maximize availability to patients, consider novel secondary end points, and study patients with newly diagnosed disease. Lastly, in order to minimize delays in developing novel therapies and promote the most efficient use of research resources and patient samples, data sharing should be incentivized.

Malignant peripheral nerve sheath tumor (MPNST) is an aggressive soft tissue sarcoma associated with dismal clinical outcomes. The risk of MPNST is dramatically increased in individuals with neurofibromatosis type 1 (NF1). In 2002, an international consensus meeting on NF1-associated MPNSTs (1) emphasized the importance of a multidisciplinary approach,

molecular genetic studies to identify patients at high risk, development of an international database and tumor bank, new imaging methods, and the need for targeted therapies. Although the clinical outcome for MPNST has not changed substantially in the past 15 years, there has been progress in our understanding of the natural history, biology, and pathogenesis

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**Table 1.** Summary of Recommendations from “MPNST State of the Science: Outlining a Research Agenda for the Future” (October 2016 conference at the National Institutes of Health, Bethesda, MD)\*

Topic	Key research recommendations
Diagnosis, imaging, and primary management	Development of: <ol style="list-style-type: none"> <li>1) standardized FDG-PET and MRI imaging guidelines;</li> <li>2) cost-efficient whole-body MRI imaging protocols and prospective trials of their value in MPNST detection;</li> <li>3) prospective trials evaluating the role of chemotherapy and radiation potentially in combination with immunotherapy or other targeted agents on survival in MPNST.</li> </ol>
Pathology	Investigation of: <ol style="list-style-type: none"> <li>1) the histology and immunohistochemical features associated with transformation of plexiform neurofibroma to MPNST;</li> <li>2) the pathobiology, genetics, and histology of atypical neurofibromatous neoplasms of uncertain biologic potential (ANNUBP);</li> <li>3) clinical behavior of ANNUBPs vs low-grade MPNSTs, ideally from patients with preoperative imaging and long-term follow-up.</li> </ol>
Genomics and biomarkers	Development of: <ol style="list-style-type: none"> <li>1) a centralized database of comprehensive, standardized clinical data from MPNST subspecialty centers;</li> <li>2) a mechanism for prospective MPNST and precursor sample collection from NF1 and sarcoma clinical trial groups;</li> <li>3) single-cell sequencing methodologies to define the extent and clinical significance of MPNST intratumoral heterogeneity.</li> </ol>
Preclinical models	Development of: <ol style="list-style-type: none"> <li>1) a central repository of DNA-fingerprinted MPNST lines;</li> <li>2) zebrafish MPNST models;</li> <li>3) mouse models to study the plexiform neurofibroma to MPNST transition, MPNST metastasis, and drug resistance;</li> <li>4) patient-derived xenograft models.</li> </ol>
Clinical trial methodology	Development of: <ol style="list-style-type: none"> <li>1) historical controls using baseline time-to-progression data from completed studies to inform future MPNST trials;</li> <li>2) novel trials for patients with newly diagnosed and fully resectable MPNST;</li> <li>3) novel trial designs that minimize regulatory requirements and maximize enrollment efficiency, eg, multiple-arm studies of new agents or combination therapies.</li> </ol>
MPNST “hackathon”	Incentivization of the MPNST community to: <ol style="list-style-type: none"> <li>1) combine existing published and unpublished data;</li> <li>2) develop a core set of questions that articulate the key problems in MPNST;</li> <li>3) foster a collaborative research environment.</li> </ol>

\*ANNUBP = atypical neurofibromatous neoplasms of uncertain biologic potential; FDG-PET = fluorodeoxyglucose-positron emission tomography; MPNST = malignant peripheral nerve sheath tumor; MRI = magnetic resonance imaging; NF1 = neurofibromatosis type 1.

of these cancers. These insights, combined with the availability of next-generation sequencing technologies and preclinical MPNST models, hold great promise to improve outcomes for patients with or at risk for MPNST.

In 2016, a second international meeting titled “MPNST State of the Science: Outlining a Research Agenda for the Future” was convened to address how recent advances can be translated into novel therapies and prevention strategies. In preparation for this meeting, the state of MPNST research was reviewed (2). The conference then divided into five working groups: diagnosis, imaging, and primary management; pathology; genomics and biomarkers; preclinical models; and clinical trials methodology. Working group members (listed in the [Supplementary Materials](#), available online), were charged with developing group-specific research priorities for the next five to 10 years. The proposed priorities were then discussed and refined by the participants in the entire conference. In addition, a keynote speaker and invited panel of data science experts discussed how data-intensive, novel problem-solving approaches (eg, a “hackathon”) can be applied to MPNST. This report and [Table 1](#)

summarize the consensus of the individual working groups for research priorities in NF1-associated MPNST.

## Diagnosis, Imaging, and Primary Management

The group agreed that complete surgical resection with wide negative margins is the optimum management of high-grade MPNST and that early diagnosis and potential prevention of MPNST should be prioritized.

## Diagnosis

Heightened surveillance is required when risk factors for MPNST are present. These include whole NF1 gene deletion, family history of MPNST, prior radiation therapy, large plexiform neurofibroma burden or multiple distinct nodular lesions on magnetic resonance imaging (MRI), neurofibromatous neuropathy, and atypical neurofibroma(s). Painful, firm, and rapidly-growing masses require investigation for potential

malignancy. MRI and fluorodeoxyglucose-positron emission tomography (FDG-PET) imaging have a role in the diagnosis of malignant transformation. Standardization of imaging protocols is needed to define the diagnostic utility of both approaches and to permit meaningful comparisons across institutions. Whole-body MRI (WBMRI) is potentially useful to detect MPNST and for surveillance after therapeutic intervention, but WBMRI protocols are needed that are cost-efficient and covered by insurance carriers (imaging studies are billed based on number of body parts imaged in many institutions).

It was concluded that a diagnostic biopsy is required for masses concerning for high-grade MPNST to facilitate optimal surgical planning. Ideally these biopsies should be performed or directed by the team performing the surgery. Conversely, a mass likely to be a low-grade/atypical neurofibroma may not require biopsy prior to resection because this would not affect surgical management.

## Management

There was consensus that precursors for MPNST (atypical neurofibroma and low-grade MPNST) should be surgically resected if they can be easily removed with low potential for morbidity. Resection with wide margins is not necessary, and preservation of neurological function is of paramount importance.

The pathology working group removed the diagnosis of “low-grade MPNST” because it cannot be differentiated from atypical neurofibroma. Nonetheless, participants recommended standardization of detailed pathology reports commenting on cellularity, number of mitoses, and degree of atypia to facilitate clinical correlation.

The management of deep-seated, concerning masses or of multiple potential MPNSTs is challenging and should be guided by pain, tumor growth, functional impairment, FDG avidity, MRI characteristics, and interval change.

There was no consensus on the use of chemotherapy for MPNST, and there are no prospective data on the effect of chemotherapy on survival. Radiation oncologists and oncologic surgeons agreed that radiation should be administered to large, high-grade MPNST, ideally in the preoperative setting when expected toxicity is lower and a smaller radiation field can be used.

Research priorities identified by the group include the development of 1) standardized FDG-PET and MRI imaging guidelines for evaluation of masses concerning for MPNST; 2) prospective studies analyzing the potential value of WBMRI in the detection of MPNST, which could be combined with a detailed prospective study of individuals at high risk for malignant transformation of neurofibromas, including clinical manifestations, imaging, and genomic characteristics of tumor samples correlated with diagnostic and interventional modalities; 3) WBMRI cost-efficient imaging protocols; and 4) prospective trials evaluating the role of chemotherapy and radiation therapy, potentially in combination with immunotherapy or other targeted therapy on survival in MPNST.

## Pathology

Pathologists can almost always classify cases of peripheral nerve sheath tumors in NF1 patients as either benign or malignant using histologic evaluation and immunohistochemical studies. For those rare borderline or atypical masses that are

difficult to classify, there is a lack of evidence to support a unifying standardized workup. With the overarching goal to avoid overtreatment of nonmalignant peripheral nerve sheath tumors (and undertreatment of malignant ones) in NF1 patients, the pathology working group proposes guidelines to define subsets of borderline lesions that will require validation.

Neurofibroma with cytologic atypia in the absence of increased mitotic activity is a nonmalignant process. However, neurofibromatous tumors containing various combinations of high cellularity, nuclear atypia, and low mitotic activity of less than 3/10 high-power fields (HPFs) are of uncertain biologic potential. They overlap with tumors often designated, especially in the past, as low-grade MPNSTs (3).

In contrast, MPNST is defined by high cellularity, nuclear atypia, usually brisk mitotic activity (>10/10 HPFs), and often tumor necrosis. Tumors with only some of these criteria and lower mitotic rates may represent an intermediate category that needs validation. Biomarkers that may prove helpful in highlighting the transformation of a neurofibroma into an MPNST include the following:

- Schwannian cell lineage markers S100/Sox10: often lost in malignant transformation;
- CD34 fibroblastic framework: often lost in high-grade MPNST;
- Ki67 greater than 10%: suggests malignancy;
- p16/CDKN2A loss: a step in transition from plexiform neurofibroma to MPNST, occasionally observed in histologically defined neurofibroma;
- H3K27me3: variably observed loss in MPNST;
- TP53: extensive positivity suggests high-grade MPNST.

To clarify the biologic potential of atypical neurofibromatous neoplasms of uncertain biologic potential (ANNBP), the pathology working group proposes a retrospective study of borderline malignant nerve sheath tumors diagnosed either as atypical neurofibromas/nerve sheath tumors or low-grade malignant MPNSTs. To improve the clinical correlation, the tumors will be selected from patients with preoperative imaging and long-term clinical follow-up. It is anticipated that the results of this study will give better guidance to surgeons and other clinicians for optimal management of borderline malignant peripheral nerve sheath tumors in NF1. In some cases, a better understanding of biologic potential may direct surgeons to more appropriate resections with respect to surgical margins.

## Genomics and Biomarkers

Participants in the Genomics and Biomarkers session considered the results of other successful large-scale collaborative efforts within the NF1 research community, such as the NF1 Optic Pathway Glioma (NF1-OPG) Task Force, the Children’s Tumor Foundation (CTF) Synodos NF1 Low-Grade Glioma (LGG) Consortium, and the International NF1 Autism Collaborative Team (INFACT) project (4). The NF1-OPG Task Force project built upon single-site (5) and multi-institution clinical sample aggregates (6,7) to establish that female sex and glioma brain location are important predictors of clinical outcome. Similarly, the power of the INFACT study, which included existing data from over 530 subjects from six clinical centers worldwide, was the ability to uncover important features of NF1-related autism not possible when smaller individual site cohorts were employed.

Modeled on these successes, similar adequately powered efforts may reveal previously unrecognized, but clinically

useful, prognostic clues about MPNST natural history and biology. The participants in this session proposed three research priorities. First, to determine the natural history and phenotypes of NF1-associated MPNST and precursor lesions (eg, atypical or nodular plexiform neurofibromas), a centralized database should be established. The goal would be to collect, in a standardized manner, histologic, immunohistochemical, molecular, radiographic, treatment, and related clinical data from centers worldwide with expertise in these NF1-related cancers. Although retrospective in nature, the resulting data from this registry may reveal previously unanticipated patterns, similar to the INFACT effort outcome. This registry would then allow the acquisition of MPNST (and precursor) biospecimens (frozen or paraffin-embedded), germline (or normal tissue DNA) samples, and any previously somatic whole-exome or whole-genome sequencing data for aggregate analyses. All data would be de-identified and shared in accordance with local institutional review board requirements. Regular follow-up, transparency, and accountability will be hallmarks of this effort. As of October 2016, 116 individuals with a diagnosis of MPNST have been entered into the CTF NF registry ([www.nfregistry.org](http://www.nfregistry.org)).

The second priority is to develop a mechanism for prospective MPNST sample collection. This will require coordination between NF1 and sarcoma clinical trial groups to maximize the capture of pathologic materials, as well as to develop uniform standard operating procedures for consent, biospecimen collection and processing, pathology review, and nucleotide extraction. A similar standardized approach was recommended to facilitate the collection of serum and/or plasma samples for biomarker studies. For sample tracking and storage, the biobank could either be a physical, centralized entity (eg, the CTF biobank) or a decentralized, virtual one (eg, a catalog of available samples at different institutions). Consideration should also be given to the use of “crowdsourcing” (eg, social media) as a recruitment tool.

The third priority is the use of single-cell sequencing methodologies to define the extent and clinical significance of MPNST intratumoral heterogeneity. Multiple analytic platforms, including those that employ DNA, RNA, methylation (epigenetics), and microRNA analyses, are needed. In this manner, the identification of clonal variation within these malignancies may yield important insights into the evolution of metastasis and the mechanisms that underlie therapeutic resistance.

## Preclinical Models

Since the last consensus meeting, robust models of MPNST have been developed, and their advantages and disadvantages in discovery and translational research were discussed. Opportunities for discovery research in MPNST that were discussed included identification of MPNST-specific cell surface proteins, circulating antigens and DNA for liquid biopsies, and drug resistance mechanisms.

Translational studies for MPNST are either performed in xenografts of human cell lines into immunocompromised mice, in patient-derived xenograft (PDX) models, or in genetically engineered animal models (2). To avoid misidentification of MPNST cell lines due to lapses in quality control and documentation, the group recommended DNA fingerprinting and deposition of MPNST lines in a central repository. PDX models (2) may be more predictive than cell line xenografts of patient responses to treatment, although this requires more rigorous testing. PDX models of MPNSTs have been challenging to generate but now

exist (8), and they should be characterized and made available through a central repository to ensure quality control.

Nf1-mutant models in yeast (IRA1/2) (9), fly (10), slime mold (11), and zebrafish (12) have been reported. Zebrafish Nf1 mutants develop fish MPNST when crossed to other mutations and may be useful for preclinical drug screening (13). Participants supported further development of zebrafish MPNST models and incentivizing collaborations between NF1 and zebrafish research communities. Genetically engineered mouse models (GEMMs) (2) harboring mutations in Nf1 and Trp53 develop MPNSTs with concomitant changes in the micro-environment and are currently being routinely used in preclinical drug testing. At least nine Nf1-mutant MPNST GEMMs have been reported in the literature to date, with differences in grade, latency, and penetrance (2). An updated pathology review of MPNST GEMMs is needed to compare models with patient MPNSTs. Although robust plexiform neurofibroma (PNF) models exist, the PNF-to-MPNST transition has not yet been modeled in GEMMs. A model of this transition would facilitate studies of tumor progression mechanisms and would be useful for preclinical testing of MPNST prevention. Validated models of MPNST metastasis are also needed.

We recommend that preclinical drug testing for MPNST continue to use a “funnel” approach. Candidate drugs (or combinations) should be screened in cultured MPNST cells, or model organisms with short generation times, and studied for cell-based mechanisms of action, such as cytostasis and/or cytotoxicity. Promising candidates should be screened in “medium-throughput” (zebrafish or mouse) vertebrate platforms for general toxicity, tumor drug delivery, and in vivo effects on tumor cells. Finally, top candidates should be tested in a GEMM model: ideally, a mammalian system with an imprinted genome, intact immune system, and co-evolution of the stroma and tumor.

The group recommends three ways to improve the use of mouse models in preclinical trials. First, response criteria in mice should be set as rigorously as in clinical trials, including determining pharmacodynamics and pharmacokinetics of candidate drugs. Second, tumors need to be well established (at least 150 mm<sup>3</sup>) to begin treatment trials, and researchers should examine the durability of response and recurrence (if any) of tumor growth after discontinuing therapy. Lastly, experimental results using these rigorous criteria should guide moving candidate drugs into clinical trials.

## Clinical Trials Methodology

The challenges in the clinical development of effective treatments in MPNST include optimizing end points to increase the accuracy and efficiency of clinical trials, assimilation of end points across preclinical and clinical trials, specific study designs for the various stages of MPNST evolution, and increasing the efficiency of opening and completing clinical trials in this ultrarare disease. Participants of the clinical trials methodology working group prioritized and addressed these challenges.

Optimized end points permit more accurate and efficient clinical trials. To date, clinical trials in MPNST (14–19) have used imaging end points with MRI or CT using WHO (20), RECIST (21), or Choi criteria (22). Functional imaging, such as FDG-PET and magnetic resonance imaging apparent diffusion coefficient (MRI ADC), and patient-reported outcomes, such as pain, should be considered secondary end points to evaluate whether these modalities can be incorporated as part of outcome measurements. To date, clinical trials with noncytotoxic, targeted



therapies for unresectable/recurrent MPNST have yet to demonstrate an objective response using the traditional measures noted above. The clinical benefit rate (CBR) has been recently proposed as an end point. CBR is the sum of objective responses and prolonged stable disease. Multiple negative phase II studies for MPNST have been published or completed. Although disappointing, there is a great opportunity to compile and analyze the completed studies to develop a baseline time to progression that can be used as a high-quality, relevant historical comparison for future MPNST phase II trials targeting recurrent disease.

The focus of most clinical trials in MPNST has been in the setting of recurrent or unresectable disease. Finding therapies for this group of patients with no known curative treatments is a priority, and knowledge gained would translate to all MPNST patients. However, the cohort of patients with newly diagnosed and fully resectable MPNST has historically not been well studied; from this group, we can potentially learn to effectively treat and thus prevent recurrent disease. An additional consideration for trials in people with newly diagnosed MPNST is that this would more faithfully represent the preclinical study designs, possibly allowing for more direct clinical translation.

For low-grade MPNST and atypical neurofibromatous neoplasms of uncertain biologic potential where surgery is planned and there is no indication for neoadjuvant radiotherapy or chemotherapy, phase 0 trials can be utilized for proof of concept of target inhibition and biomarker development. For newly diagnosed patients recommended to have neoadjuvant chemotherapy, combination studies with “standard” chemotherapy, such as doxorubicin and ifosfamide with novel agents compared with historical control from the SARC006 study (23), could also be developed.

Finally, experience from prior cooperative group MPNST studies has shown that the time to open one clinical trial can be upwards of two years, in part because of costs and regulatory requirements. However, even for an ultrarare disease, accrual into MPNST trials is rapid once a study opens. Hence there is motivation for trial designs that minimize regulatory requirements and maximize availability to patients. The CTF and Neurofibromatosis Therapeutic Acceleration Program (NTAP) sponsors the preclinical NF consortium. This NF preclinical platform conducts preclinical drug trials to identify agents for further study in clinical trials and has been very productive (115 preclinical trials to date), delivering several viable agents (16 drugs) to the clinical pipeline, including the highly successful MEK inhibitors. Multiple-arm studies of new agents (or combinations of agents), each guided by preclinical data, should open in parallel or sequentially, with outcome compared with historical controls. Such novel designs and forward thinking are needed to move this field forward, and ultimately find more effective treatment for MPNST.

## Creating Greater Research Synergy: The Potential of a “Hackathon” to Solve Critical Problems in MPNST

Dr. Shasha Jumbe of the Gates Foundation served as the keynote speaker and invited the group to consider a “hackathon” to catalyze data science innovation and analyze increasingly plentiful genomic data and to generate new hypotheses for future research. In a “hackathon” or “data jam,” data scientists and coders (the “crowd”) are invited to apply novel data exploration and data analysis methods on curated and harmonized open source data to solve complex problems in a sprint-like event. Recent successful examples include a crowdsourced prostate cancer prediction tool (<http://sagebase.org/in-the-news/pros>

tate-cancer-challenge-crowdsourcing-a-better-prostate-cancer-prediction-tool/) and a contest to improve breast cancer detection through deep machine learning ([https://www.synapse.org/Digital\\_Mammography\\_DREAM\\_Challenge](https://www.synapse.org/Digital_Mammography_DREAM_Challenge)).

In 2014, to capitalize on available genomics data, the CTF entered into a partnership with Sage BioNetworks to launch the first ever NF data hub. Participants of all CTF-sponsored team science programs (Synodos) are required to deposit their raw data with Sage BioNetworks. The scientists at Sage have built the platforms and analysis tools and integrated the cross-disciplinary data sets in collaboration with the Synodos team members. Additionally, other funders such as the National Cancer Institute and NTAP deposit their data into this data hub.

To maximize the use of MPNST-associated data in a future hackathon, the MPNST community should continue to share and combine existing data (including published and unpublished variables) and assess if they are of sufficient quality and quantity. The community should develop a core set of questions that articulate the key problems in MPNST. Initial query-driven analyses on available data should direct which data gaps to fill, and funders will be invited to formulate a strategy to enrich the data set. Importantly, not all valuable questions lend themselves to hackathon sessions. Lastly, to be successful, a collaborative research environment needs to be created that fosters success and incentivizes data sharing. This requires attention to issues of authorship, attribution and ownership, funding, availability of appropriate analytic and visualization tools, common data infrastructure and storage, and harmonization methods for data and metadata. Taken together, the NF1-MPNST community is currently uniquely positioned to establish such a consortium with a high likelihood of transforming the care of individuals with these deadly cancers.

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